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Inflammation, oxidative stress and postoperative atrial fibrillation in cardiac surgery

M. Zakkar [a], R. Ascione [a], A.F. James [b], G.D. Angelini [a], M.S. Suleiman [a,*]

[a] Bristol Heart Institute, University of Bristol, Level 7, Bristol Royal Infirmary, Upper Maudlin Street, Bristol BS2 8HW, UK
[b] School of Physiology & Pharmacology, University of Bristol, Medical Sciences Building, University Walk, Bristol, BS8 1TD, UK

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ABSTRACT

Postoperative atrial fibrillation (POAF) is a common complication of cardiac surgery that occurs in up to 60% of patients. POAF is associated with increased risk of cardiovascular mortality, stroke and other arrhythmias that can impact on early and long term clinical outcomes and health economics. Many factors such as disease-induced cardiac remodelling, operative trauma, changes in atrial pressure and chemical stimulation and reflex sympathetic/parasympathetic activation have been implicated in the development of POAF. There is mounting evidence to support a major role for inflammation and oxidative stress in the pathogenesis of POAF. Both are consequences of using cardiopulmonary bypass and reperfusion following ischaemic cardioplegic arrest. Subsequently, several anti-inflammatory and antioxidant drugs have been tested in an attempt to reduce the incidence of POAF. However, prevention remains suboptimal and thus far none of the tested drugs has provided sufficient efficacy to be widely introduced in clinical practice. A better understanding of the cellular and molecular mechanisms responsible for the onset and persistence of POAF is needed to develop more effective prediction and interventions.

Contents

1. Introduction

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterised by uncoordinated atrial activation with ensuing deterioration of mechanical function (Potpara & Lip, 2011; Andrade et al., 2014; Weijs et al., 2014). Post-operative AF (POAF) is a common complication (typically occurring within the first 2 to 3 days) after cardiac surgery with an incidence up to 60% depending on the type of surgery (coronary artery bypass graft surgery, valve surgery, or combined) (Maisel et al., 2001; Ascione et al., 2002; Mostafa et al., 2012; Orenes-Pinero et al., 2012; Hernandez-Romero et al., 2014). Patients with POAF have increased risk of cardiovascular mortality, stroke and other arrhythmias than patients without POAF (El-Chami et al., 2010; Mostafa et al., 2012; Brooks & Schindler, 2014; Philip et al., 2014).

Pre-existing co-morbidities, operative trauma, ischaemia and reperfusion injury during surgery, changes in atrial pressure due to postoperative ventricular stunning, chemical stimulation and reflex sympathetic/parasympathetic activation have all been identified as contributing factors (Maisel et al., 2001; Ferro et al., 2009; Maesen et al., 2012; Mostafa et al., 2012). The incidence of POAF differs between

Abbreviations: AF, atrial fibrillation; ATP, adenosine triphosphate; CA, cardioplegic arrest; CPB, cardiopulmonary bypass; CABG, Coronary artery bypass grafting; CRP, C-reactive protein; IL, interleukin; LVH, left ventricle hypertrophy; MAO, monoamine oxidase; MS, metabolic syndrome; mPTP, mitochondrial permeability transition pore; MAPK, mitogen-activated protein kinase; NADPH, nicotinamide adenine dinucleotide phosphate; NRF2, nuclear factor, erythroid 2-like 2; NF-KB, nuclear Factor-KB; n-PUFAs, n-3 polyunsaturated fatty acids; POAF, postoperative atrial fibrillation; ROS, reactive oxygen species; RBC, red blood cells; GSHt, total glutathione; TGF-β1, transforming growth factor-β1; TNF-α, tumour necrosis factor α; VWF, Von Willebrand factor.

* Corresponding author at: School of Clinical Sciences and the Bristol Heart Institute, University of Bristol, Bristol Royal Infirmary, Upper Maudlin Street, Bristol BS2 8HW, UK. Tel.: +44 117 3423519.
E-mail address: m.s.suleiman@bristol.ac.uk (M.S. Suleiman).

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different forms of cardiac surgery, indicating that the pro-arrhythmia depends on processes triggered by the surgical intervention itself (Creswell et al., 1993). However, little is known about the cellular and molecular mechanisms responsible for the onset or perpetuation of POAF. What is known however is that POAF has some pro-arrhythmic mechanisms in common with other forms of AF as supported by data demonstrating that patients who develop POAF have a degree of structural remodelling evident by a larger left atrium, a tendency towards having larger left atrial appendage dimension, and lower left atrial ejection fraction. Additionally, those patients tend to have increased atrial conduit function, and evidence of left ventricular diastolic relaxation impairment compared to those without AF (Aytemir et al., 1999; Nakai et al., 2002; Leung et al., 2004; Ferro et al., 2009; Maesen et al., 2012; Nardi et al., 2012). Other abnormalities that have been associated with increased incidence of POAF include high pre-operative levels of cholesterol (Aydin et al., 2014). Relevant to this is the finding that metabolic syndrome (MS) is an independent predictor of POAF (Brown & Moukdar, 2013; Hurt et al., 2013; Montaigne et al., 2013). MS represents a cluster of metabolic events related to various degrees of insulin resistance such as central obesity and hypertension, thus increased risk of developing type 2 diabetes mellitus. Mitochondrial dysfunction in patients with MS has been linked to the development of arrhythmias (Montaigne et al., 2013), possibly mediated by increased sensitivity to calcium-induced mitochondrial permeability transition pore (mPTP) opening.

Finally, POAF has in recent years been closely linked to pro-inflammatory mediators and oxidative stress. The level of inflammation and oxidative stress is related to the pre-operative status and to the triggers associated with cardiac surgery (Fig. 1). This review will focus on the role of inflammation and oxidative stress in the pathogenesis of POAF and their potential as therapeutic targets.

2. Origins of inflammatory response during open heart surgery

The inflammatory response during cardiac surgery is largely due to the operative trauma involving surgery, CPB and organ reperfusion injury. However, a less known source of inflammatory response is associated pre-operative cardiovascular disease state.

2.1. Inflammatory state prior to surgery

Patients undergoing open heart surgery are likely to have a pre-operative chronic inflammatory state that can be triggered by cardiac disease and co-existing co-morbidities. For example there is a close link between atherosclerosis and inflammation where atherosclerosis is considered an inflammatory disease (Anogeianaki et al., 2011). Furthermore, there is strong experimental evidence to suggest that atherogenic stimuli (e.g., diabetes, dyslipidaemia) do in fact trigger vascular inflammatory response which indirectly contributes to stable atherosclerotic disease and that plaque disruption is triggered by subsequent inflammatory stimuli (Libby & Crea, 2010; Libby, 2012). The source of the inflammatory response is not necessarily systemic as ischaemic disease-induced cardiac remodelling can in principle produce a local inflammatory response as supported by work showing that hypoxic cardiomyocytes produce cytokines (Sawa et al., 1998). One reason for the fact that this chronic disease-related inflammatory response has not received much attention from the scientific community could be the relatively low levels of circulating inflammatory markers. However, this is likely to be more relevant following an acute infarction as has been demonstrated in experimental models (Deten et al., 2002; Deten & Zimmer, 2002). In clinical settings, cytokines including IL6 are acutely elevated during ST- or non-ST-elevation acute coronary syndromes (Neumann et al., 1995; De Servi et al., 2014). Markers of inflammation are also elevated in heart failure which can be reduced by cardiac resynchronization therapy (Rubaj et al., 2013).

2.2. Systemic Inflammatory response during surgery

The main inflammatory response seen during cardiac surgery (both systemic and non-systemic) is associated with the surgery itself. An acute systemic inflammatory response is initiated by a number of injurious processes including surgical trauma, CPB and organ reperfusion injury (Paparella et al., 2002). CPB is a major trigger of inflammatory response during cardiac surgery since off-pump surgery has been shown to significantly reduce inflammatory response (e.g. (Ascione et al., 2000; Caputo et al., 2002; Nesher et al., 2006)). CPB can impact upon the cellular and non-cellular elements of blood resulting in the activation of different pro-inflammatory cascades (Hill, 1998; Anselmi et al., 2004; Khoynezhad et al., 2004; Rinder, 2006; Suleiman et al., 2008). It is now generally accepted that CPB is a direct trigger of cardiac injury since miniaturized cardiopulmonary bypass is associated with less cardiac injury compared to conventional bypass (Remadi et al., 2006; Skrabal et al., 2007; El-Essawi et al., 2010; Nguyen et al., 2014). More importantly, miniaturized cardiopulmonary bypass is associated with less inflammatory response (van Boven et al., 2004; Remadi et al., 2006; Skrabal et al.,

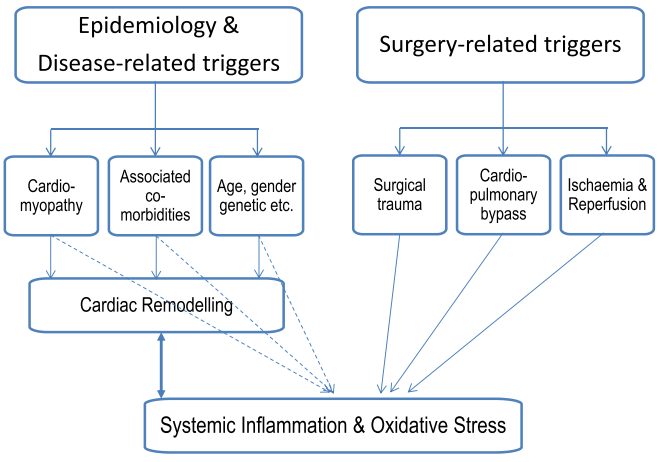

Fig. 1. Flow chart showing the source of inflammation & oxidative stress pre-and postoperatively. See text for details.

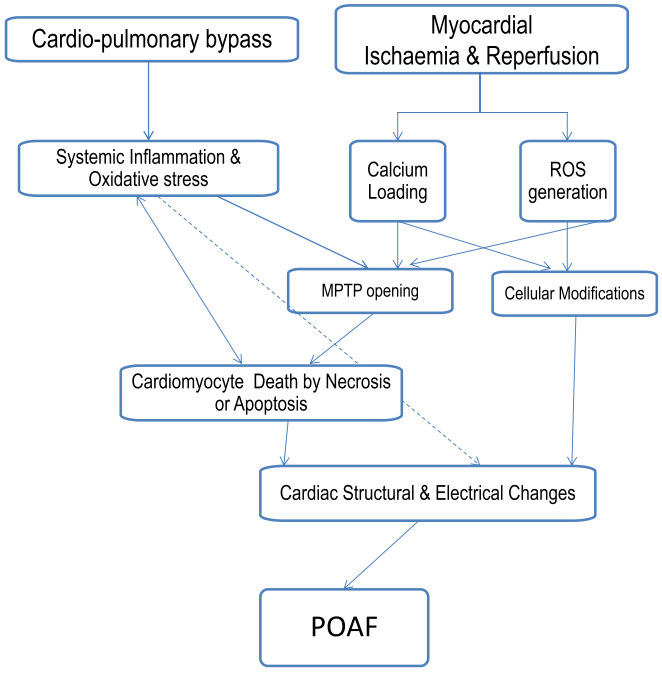

Fig. 2. Flow chart showing the effect of CPB and ischaemia and reperfusion on cardiac remodelling that can lead to POAF.

2007). In addition to CPB, several associated factors including hypothermia, haemodilution, electrolyte imbalance, pharmacological agents used during surgery have also been implicated in initiating inflammatory responses and triggering tissue injury (Asimakopoulos, 2001; Levy & Tanaka, 2003; Iriz, 2004; Rinder, 2006). However, myocardial ischaemic cardioplegic arrest and reperfusion has been implicated as a major trigger of tissue damage and inflammatory response (Fig. 2).

2.3. Inflammatory response associated with myocardial ischaemia and reperfusion

Cardiomyocytes exposed to ischaemia–reperfusion or hypoxia–reoxygenation produce IL-6 (Sawa et al., 1998; Chandrasekar et al., 1999). This cytokine is also produced by the myocardium during ischaemic cold cardioplegic arrest in an experimental model of cardiopulmonary bypass (Dreyer et al., 2000). Myocardial release of IL6 can be seen during cardiac surgery on CPB as early as 10 min after reperfusion and this release continues and increases throughout the reperfusion period (Zahler et al., 1999). It is suggested that cardiac endothelial cells or macrophages are responsible for early release whilst cardiomyocytes could be responsible for latter release. Other pro-inflammatory cytokines produced by the heart during cardiac insults include IL-18 and IL-1β (Matsumori et al., 1999; Pomerantz et al., 2001). IL-1 is produced in response to local or systemic stimuli (Dinarello et al., 2012) and is responsible for cardiac dysfunction in heart failure and the effect is mediated by IL-18 (Toldo et al., 2014). It is also important to note that heart cells produce IL-10 (Jones et al., 2001). This is an anti-inflammatory cytokine involved in the limitation and termination of inflammatory responses (Asadullah et al., 2003). It is evident therefore that the myocardium is a source of pro- and anti-inflammatory markers particularly during ischaemia and reperfusion. In addition to systemic inflammatory response contributing to cardiac injury (see above), there is also mounting evidence showing that this response (systemic and/or cardiac origin) can directly alter cardiac function, possibly mediated by the action of cytokines on membrane receptors of cardiomyocytes.

3. Inflammatory response and the pathogenesis of postoperative atrial fibrillation

3.1. The effect of inflammatory mediators on cardiac function

The effects of cytokines will depend on whether they are pro-inflammatory or anti-inflammatory ones. It has been suggested that IL-6 is capable of modulating cardiovascular function by a variety of mechanisms, including promotion of left ventricular remodelling (Pagani et al., 1992), induction of contractile dysfunction (Yokoyama et al., 1993), and altering the response of myocardial β-adrenergic receptors (Gulick et al., 1989). More importantly, IL-6 has been associated with negative inotropic effects (Finkel et al., 1992) and myocardial stunning (Zahler et al., 1999). These effects could be due to enhanced production of nitric oxide (NO) and elevated cGMP (Stangl et al., 2002) which would inhibit voltage dependent Ca^{2+} channels (Kojda et al., 1999). Others (Dreyer et al., 2000) have implicated IL-6 in cardioprotection by inhibiting cardiac myocyte apoptosis. Other inflammatory cytokines, particularly IL-8, can exacerbate cardiac injury by enhancing leukocyte activation and accumulation. In fact, postoperative levels of cardiac troponin-I have been shown to correlate with IL-8 levels in patients undergoing CABG surgery (Wan & Yim, 1999). Another cytokine, IL-18 has been shown to activate pro-apoptotic signalling pathways and induces endothelial cell death (Chandrasekar et al., 2004). The heart is also influenced by the anti-inflammatory cytokine IL-10 where its deficiency enhances the infiltration of neutrophils into the myocardium (Jones et al., 2001). It is evident that several of the inflammatory mediators generated in response CPB and ischaemia–reperfusion would contribute to cardiac functional depression and apoptosis (Wang et al., 2005). These cardiac changes could alter electrical activity and trigger arrhythmias.

3.2. Inflammatory response and factors that alter incidence of postoperative atrial fibrillation

There is mounting evidence to support the influence of a surgery-related acute inflammation on the pathogenesis of POAF. This is largely based on association between levels and activity of white blood cells and incidence of POAF. Patients who have higher postoperative leukocytes count are significantly more likely to develop POAF (Abdelhadi et al., 2004; Lamm et al., 2006; Fontes et al., 2009; Sabol et al., 2012) and patients developing POAF tend to have greater degree of monocyte activation as seen by higher expression of CD11b (Fontes et al., 2005). Moreover; the elevated pre and post-operative neutrophils/lymphocytes ratio in patients undergoing CABG can be associated with an increased incidence of POAF (Gibson et al., 2010). Exactly how these blood components can trigger POAF is not known. Previous work using animal models has shown that when activated neutrophils bind to cardiac myocytes they can cause changes in myocyte electrical activity that could be arrhythmogenic (B. F. Hoffman et al., 1997). Ischaemic stress is potentially arrhythmogenic as supported by work demonstrating that isopreternol-isoproterenol-induced atrial ischaemic stress (fall in atrial ATP) produced a pro-arrhythmic substrate such that atrial tachyarrhythmia could be induced by burst-pacing (S. J. Kim et al., 2012).

CPB and surgical trauma can lead to the production of different pro-inflammatory mediators alongside widespread endothelial activation with increased expression of adhesion molecules and impaired release of nitric oxide. Increased levels of IL-6, TNF-α and CRP have all been associated with POAF (Ucar et al., 2007; Elahi et al., 2008; Wu et al., 2013). Interestingly, eliminating the use of CPB (off pump) may not fully attenuate the incidence of POAF (Place et al., 2002; Siebert et al., 2003; Enc et al., 2004; Turk et al., 2007). This is likely to be due to the fact that off pump surgery is also associated with acute inflammatory responses as shown by increased post-operative levels of IL-6 and CRP which remain predictive factors for the development of POAF in patients undergoing off pump CABG (Ishida et al., 2006). Clearly, the inflammatory response is not the only mediator of POAF and the threshold and the type of inflammatory response needed to augment incidence of POAF is not presently known. In this respect it would be interesting to find out whether the incidence of POAF is also influenced by valve surgery as ischaemic coronary disease (atherosclerosis) may have a different effect on the inflammatory response. Ultimately, it is the inflammatory response within the atrial tissue (remodelling) that might be critical in determining the onset of POAF. When investigating the expression of different pro-inflammatory markers in the left and right atrial appendage it was noted that the intensity of VWF expression in left atrial appendage tissue predicted patients who developed POAF after CABG (Kaireviciute et al., 2011). TGF-β1 have also been implicated in the pathology of AF in animal models. However, it is not known whether this elevation is the trigger or the consequence of AF. Analysis of human right atrial tissue has demonstrated the presence of higher levels of total and active TGF-β1 in patients who developed POAF compared to patients remaining in sinus rhythm. The impact of TGF-β1on the development of POAF may be related to the possibility that the factor can promote the expression of fibrosis-related genes in a Smad2 related pathway (Rahmutula et al., 2013). Hence, more work is warranted in this area to establish whether atrial tissue inflammatory response does in fact play an important role in the pathogenesis of POAF. In particular it would be interesting to establish whether inflammation triggers atrial remodelling and changes in Ca^{2+} cycling as both these factors are implicated in triggering arrhythmias (Heijman et al., 2014). It is interesting to note that the principal metabolite of the ryanodine receptor modulator, K201, has an anti-arrhythmic action against paroxysmal AF in the canine sterile pericarditis model of post-operative AF associated with inflammation (Page et al., 1986; Kumagai et al., 2004; Rossman et al., 2009; Zhang et al., 2011; Sadrpour et al., 2015).

4. Oxidative stress during open heart surgery

Physiological redox signalling refers to the role of reactive oxygen species (ROS) in intra- and intercellular communication (Collins et al., 2012). Oxidative stress occurs when there is significant uncontrolled generation of ROS that overwhelm endogenous anti-oxidant capabilities. Like inflammatory response (see above) pre-operative disease states (e.g. ischaemia, diabetes, and atherosclerosis) are also associated with oxidative stress (Giustarini et al., 2009). ROS are generated during open heart surgery using CPB and CA. Main sources of elevated ROS are associated with changes at both systemic and myocardial level.

4.1. Systemic reactive oxygen species production during surgery

The inflammatory response seen during CPB is in part responsible for generating ROS and increased oxidative stress during cardiac surgery (McDonald et al., 2014). It exposes RBCs to non-physiological stimuli modifying their integrity and role. CPB can damage RBC due to shear stress forces which make RBC less deformable and more fragile (Hoffman, 1962; Morariu et al., 2004), thereby resulting in more free Hb in circulation (Baskurt & Meiselman, 2003; Morariu et al., 2004; Saraf et al., 2009; Zakkar et al., 2015). Furthermore; peri-operative blood transfusion can result in increased oxidative stress when stored blood is used due to diminish antioxidant properties or storage defect which is evident from ATP and 2,3-diphosphoglycerate depletion and increased lipid peroxidation (Relevy et al., 2008; Karkouti, 2012; Zakkar et al., 2015).

4.2. Myocardial reactive oxygen species production during surgery

Although cardiomyocytes are considered a major source of ROS in the injured myocardium, it is important to note that ROS can also be generated by vascular endothelial cells and activated leukocytes involving NADPH oxidase and/or xanthine oxidase (Tsutsui et al., 2011). The main trigger of ROS generation in the myocardium is reperfusion injury (Suleiman et al., 2008; Suleiman et al., 2011). Ischaemia during cardiac surgery is associated with reduced mitochondrial energy production which can lead to changes in intracellular Na^+, Ca^{2+} and pH (Suleiman et al., 2001; Murphy & Steenbergen, 2008; Suleiman et al., 2008). Ischaemic injury can lead to the accumulation of activated neutrophils in the myocardium resulting in the release ROS and other proteolytic enzymes (Suleiman et al., 2008). Further myocardial damage can occur during reperfusion as a consequence of mitochondrial dysfunction driven by ROS production (Wang et al., 2005; Suleiman et al., 2011). The opening of the mPTP due to ROS production will result in further ROS production and leads to mitochondrial swelling, mitochondrial membrane damage and cell death (Connern & Halestrap, 1994; Halestrap et al., 2004; Honda et al., 2005; Pasdois et al., 2011). Moreover; high ROS levels can modulate multiple signalling pathways and transcription factors such as NF-KB, NRF2 and MAPK activation leading to inflammation, apoptosis or necrosis (Barnes & Karin, 1997; Grossmann et al., 1999; Grossini et al., 2009; Anedda et al., 2013).

4.3. Reactive oxygen species production and the pathogenesis of postoperative atrial fibrillation

Oxidative stress associated with CPB and CA is likely to trigger cellular changes in atrial tissue leading to disruption of electrical activity. The main atrial remodelling that has been linked to the pathogenesis of POAF is the ROS generating system, NADPH oxidase. Studies using right atrial appendage samples from patients undergoing CABG suggested that NADPH oxidase activity was the most important independent predictor of developing POAF (Kim et al., 2005, 2008). NADPH oxidases are a major source of ROS and have been implicated in paroxysmal and chronic AF (Kim et al., 2005; Wolke et al., 2014; Youn et al., 2013). In fibrillating myocardium, nitric oxide synthase can also contribute significantly to basal, stimulated and NADPH-stimulated superoxide release; suggesting that increased oxidative stress in this condition may lead to nitric oxide synthase uncoupling (promoting superoxide formation rather than nitric oxide) (Y. M. Kim et al., 2005). Furthermore, significant up-regulation of mitochondrial manganese superoxide dismutase activity and an increased sensitivity of mPTP opening have been demonstrated in atrial tissue from patients with triggered POAF (Montaigne et al., 2013). Moreover; measuring total glutathione (GSHt) and monoamine oxidase (MAO) in right atrial tissue suggested that POAF risk was significantly associated with MAO activity. In contrast, myocardial GSHt was inversely associated with POAF (Anderson et al., 2014).

5. The role of anti-inflammatory agents and anti-oxidants in reducing postoperative atrial fibrillation

The fact that inflammation and oxidative stress can elicit POAF has led to the undertaking of several trials using drugs with anti-inflammatory and anti-oxidant properties to try to reduce the incidence of POAF.

5.1. Statins

Statins (HMG-CoA reductase inhibitors) have proven to reduce cardiovascular events in patients at risk for adverse outcomes by lipid-lowering effects and anti-inflammatory and antioxidative stress properties (Liakopoulos et al., 2012). The ARMYDA-3 (Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery) study recruited 200 patients undergoing elective cardiac surgery with CPB and showed that treatment with atorvastatin 40 mg/day, initiated 7 days before surgery significantly reduced the incidence of POAF. Interestingly, the study supported the notion that C-reactive protein (CRP) is closely linked to POAF as patients who did not develop POAF had lower CRP levels irrespective of randomization assignment (Patti et al., 2006). A recent meta-analysis of 54 trials incorporating 91,491 patients undergoing cardiac surgery showed that preoperative statin use resulted in a significant reduction in early all-cause mortality, new onset POAF, stroke and in-hospital stay (Kuhn et al., 2014). The exact mechanisms involved in statin action are still not fully understood although statins may modulate post CPB inflammation; however, the evidence is not definitive due to multiple limitations in study design such as protocols, doses and the type of statin used (Kuhn et al., 2014).

5.2. Steroids

Multiple different clinical trials investigated the impact of steroids administration on POAF and showed that it can significantly reduce pro-inflammatory responses and the incidence of POAF (Viviano et al., 2014). Two meta-analysis of randomised clinical trials demonstrated that corticosteroid prophylaxis can significantly reduce the risk of POAF and length of stay in the ICU, postoperative bleeding and major wound infection compared with placebo (Whitlock et al., 2008; Ho & Tan, 2009).

5.3. N-3-polyunsaturated fatty acids

In addition to anti-inflammatory interventions, several studies have investigated the efficacy of anti-oxidants in reducing the incidence of POAF. Perioperative administration of n-3-PUFAs, such as those found in fish oil, have been examined with regard to preventing cardiac arrhythmias and sudden death. Although some trials had previously shown favourable effect of such fatty acids on the incidence of POAF (Calo et al., 2005; Sorice et al., 2011), recent multicentre double blind, placebo controlled, clinical trial showed that perioperative supplementation with n-3-PUFAs compared with placebo did not reduce the risk of POAF (Mozaffarian et al., 2012). It is important to note that this study

however had many limitation as it was not formally blinded, patients undergoing valvular surgery and patients with previous AF were excluded in order to avoid any possible confounding factor and patients in the n-3-PUFA group were hospitalized for significantly fewer days than those in the control group. Consequently, patients assigned to n-3-PUFA may possibly have had asymptomatic episodes of AF after discharge that were not identified. However; different meta-analysis (Mariani et al., 2013; Mozaffarian et al., 2013; Zhang et al., 2014) have confirmed the finding of this trial and showed that perioperative supplementation with n-3-PUFAs compared with placebo did not reduce the risk of POAF.

5.4. Vitamins C & E

The administration of oral vitamin C peri-operatively to patients undergoing CABG does not seem to be associated with reduced incidence of POAF (Bjordahl et al., 2012). However when used in combination with β-blockers, it was noted that it can favourably influence the incidence of POAF (Eslami et al., 2007). A systematic literature review of 5 randomised controlled trials incorporating 567 patients showed that the prophylactic use of vitamins C and E may significantly reduce the incidence of POAF and all cause arrhythmia following cardiac surgery (Harling et al., 2011). Of note, it has been reported that the combination of n-PUFAs (2 g/day) (eicosapentaenoic acid: docosahexaenoic acid ratio 1:2), vitamin C (1 g/day), and vitamin E (400 IU/day) can increase the antioxidant potential, attenuating oxidative stress and inflammation and reducing the incidence of POAF (Rodrigo et al., 2013).

5.5. Colchicine

Colchicine is a medication used for treating gout, pericarditis, familial Mediterranean fever and Behçet's disease (Ben-Chetrit et al., 2006). The anti-inflammatory effect of colchicine relates to its direct interaction with microtubules, specifically the disruption of microtubules in neutrophils (Andreu & Timasheff, 1982). Colchicine may exert effects on cytokine provoked inflammation by diminishing the qualitative expression of E-selectin on endothelium and the quantitative expression of L-selectin on neutrophils (Cronstein et al., 1995). In a randomised controlled study investigating the effect of colchicine on the prevention of early AF recurrence after pulmonary vein isolation, colchicine led to significant reductions in CRP and IL-6 levels compared to placebo (Deftereos et al., 2012). Prolonged treatment with colchicine can reduces IL-8, TNF-α and soluble E- and L-selectin levels in familial Mediterranean fever patients (Kiraz et al., 1998). Furthermore; a study in rats' renal tissue demonstrated that colchicine can prevent the increase in TGF-β expression and apoptosis (Disel et al., 2004). A recent multicentre randomized trial enrolled 360 patients undergoing cardiac surgery with the primary end point being the occurrence of post-pericardiotomy syndrome within 3 months and the main secondary end points were postoperative AF and pericardial or pleural effusion. This study showed that perioperative use of colchicine compared with placebo reduced the incidence of post-pericardiotomy syndrome but not of postoperative AF or postoperative pericardial/pleural effusion (Imazio et al., 2014). Clearly whether colchicine can be used to reduce POAF remains controversial.

5.6. N-acetylcysteine

Finally, the addition of the anti-oxidant n-acetylcysteine to cardioplegia has been shown to reduce oxidative stress and coronary endothelial activation (Rodrigues et al., 2009) and to decrease POAF incidence in patients undergoing CABG surgery (Ozaydin et al., 2013). This drug is a precursor to the amino acid cysteine which is a rate-limiting factor in glutathione production. Inclusion of cysteine in the perfusate of perfused rat heart has been shown to confer significant cardioprotection and improved preservation of ATP and glutathione (Shackebaei et al., 2005).

6. Conclusions

POAF is a common complication after cardiac surgery that can affect patients' early and long term outcomes and use of hospital resources. Inflammatory response and oxidative stress arising from pre-surgery epidemiological factors, CPB and reperfusion injury contribute to the pathogenesis of the arrhythmia, although the precise cellular mechanisms and pathways remain poorly resolved. Several anti-inflammatory agents and anti-oxidants including statins, PUFAs, steroids, Colchicine, Vitamins C and E, and acetylcysteine, have shown promising results in clinical trials. However, more work is needed before they can be routinely included in clinical practice. In particular, better understanding of atrial remodelling during surgery and its role in the development of POAF is an essential step towards developing more effective treatments and optimising conditions for therapeutic interventions that are based on anti-inflammatory agents and anti-oxidants.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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